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Propofol Based Tiva Vs. Sevoflurane Inhalation Anesthetic for Breast Cancer Surgery: A Systematic Review

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PROPOFOL BASED TIVA VS. SEVOFLURANE INHALATION ANESTHETIC FOR BREAST CANCER SURGERY: A SYSTEMATIC REVIEW

by

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Abstract

Metastasis from breast cancer leads to a higher chance of death from that cancer. According to the National Cancer Institute (2018) breast cancer survival rates among all three SEER stages (localized, regional, and distant) was approximately 90% between the years 2008 and 2014. Among these patients, those with distant metastasis had a survival rate of 27% and those with regional metastasis had an 85% survival rate (American Cancer Society, 2019). When creating an individualized anesthetic plan for a patient presenting for tumor excision of breast cancer, the anesthesia provider should create a plan that lowers the risk of metastasis and increases the patient's chance of survival. The purpose of this systematic review was to analyze which anesthetic technique, Propofol based total Intravenous Anesthesia (TIVA) or Sevoflurane based inhalation anesthetic, will elicit less immune response. A comprehensive literature review was completed using CINAHL, Medline Plus, and Pubmed Health focusing on propofol based TIVA and Sevoflurane for anesthesia maintenance for the removal of cancerous breast tumors. The PRISMA model was used to identify eligible studies. Study analysis was completed by creating study specific and data outcome tables. Critical appraisal of individual randomized control trials was performed using the Critical Appraisal Skills Programme (CASP) checklist. A cross study analysis table was also created to compare the results of all eligible studies. The findings of this systematic review determined that Propofol based TIVA increases recurrence free survival, however there is negligible differences in the immune response between Propofol based TIVA and Sevoflurane inhalation anesthetic for women undergoing surgery for breast cancer tumor excision.

Acknowledgements

To my family- thank you for all of your continued support throughout this journey. Special thanks to my husband for endlessly cheering me on and keeping me focused on my goals. Finally, I dedicate this paper to my grandfather, John Cahill D.O., an amazing anesthesiologist, grandfather, and my inspiration.

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Background/Statement of the Problem

Treatment of choice for many solid tumor cancers is excision of the tumor via surgery (Anand et al. 2015). Anesthesia plays an important role in the success, comfort, and overall surgical experience for the patient. The anesthesia provider should form an anesthetic plan that factors in the physiologic and pathophysiologic conditions of the specific patient (Nagelhout & Plaus, 2016). There is much debate about which type of anesthesia is best for patients undergoing surgery for the excision of cancerous tumors. Some studies have shown that Propofol and local anesthetics are the best choice to limit cancer metastasis Ito et al. (2017). However, many providers still choose to use a general anesthetic technique that includes the use of volatile agents such as Sevoflurane.

According to the National Cancer Institute (2018) breast cancer survival rates among all three SEER stages (localized, regional, and distant) is approximately 90% between the years 2008 and 2014. Among these patients, those with distant metastasis had a survival rate of 27% and those with regional metastasis had an 85% survival rate. This shows that the more metastasis to distant areas, the lower the chance of survival of the patient (American Cancer Society, 2019). When creating an individualized anesthetic plan for a patient presenting for tumor excision of breast cancer, the anesthesia provider should create a plan that lowers the risk of metastasis and increases the patient's chance of survival. It is hypothesized that Total Intravenous Anesthesia (TIVA) for the maintenance phase of anesthesia during surgical excision of cancerous tumors of the

breast will limit the number of immune cells released that are related to cancer metastasis.

The purpose of this study is to examine if Total Intravenous Anesthesia versus Sevoflurane is more efficacious in limiting the amounts of immune cells released during the perioperative period in breast cancer patients.

Literature Review

The literature presented here will provide general background on immunity, immune system changes that lead to cancer metastasis, breast cancer, surgeries to excise breast cancer, the impact these procedures have on the immune system, and anesthetic choice for breast cancer surgery. Immunemodulation from anesthetic choice will also be explored. Data was searched from 2002-present for this review. Search databases include CINAHL, Medline Plus, and Pubmed Health. Additional data was sought in textbooks and Google scholar with relevance to the topic.

Keywords: anesthesia, breast cancer, breast cancer surgery, immune response, immunosuppression, propofol, sevoflurane, TIVA, general anesthesia, volatile anesthetics, and survival rates.

The aim of this project is to examine if Total Intravenous Anesthesia versus Sevoflurane is more efficacious in limiting the amounts of immune cells released during the perioperative period in breast cancer patients. This topic is relevant and valuable to the discussion on anesthetic choice and its impact on immune system and overall survival of breast cancer patients. Surgery evokes a surgical stress response and with it an immune response in all patients. Anesthetics also impact the immune system. Given these contributory factors, it is important to select an anesthetic that will provide less immunocompromise to at risk populations including breast cancer patients.

Immunity

The human body is able to resist infection from organisms as well as recognize aberrant cell growth, through the immune system. Immunity falls into two classifications with some overlapping cells and processes.

The first type of immunity is innate immunity (Guyton & Hall, 2011). Innate immunity has several functions. Innate immunity phacocytizes bacteria via macrophages and white blood cells, destroys organisms though the acid that is secreted in the stomach, resists invasion or organisms through the epithelial layer, and the utilization of chemical compounds that attach to foreign organisms and or toxins (Guyton & Hall, 2011). Cells that play a role in innate immunity include epithelial cells, monocytes, macrophages, dendritic cells, natural killer cells (NK), and leucocytes. Various lymphocyte subtypes help bridge innate and acquired immunity. These subtypes include CD5-positive B-lymphocytes and γδ T-lymphocytes (Guyton & Hall, 2011).

The second type of immunity is acquired immunity. The cells involved in this branch of immunity are lymphocytes. This includes B-lymphocytes, T-lymphocytes, and natural killer cells (NK) (Eissmann, 2015). Acquired immunity works by creating genetic mutations on the B and T lymphocytes. These are expressed as antibodies and T cell receptors. When antibodies or T-cell receptors bind to antigens proliferation of antigen-specific lymphocytes occurs. A specific immune response then ensues. Each antibody binds to specific antigens. This specificity allows for selective proliferation of clonal lymphocytes that correlate with the antigen (Guyton & Hall, 2011).

Other key elements include major histocompatibility complex (MHC) and cytokines. These allow for cell-to-cell communication that is involved in both acquired and innate immunity. Another component in acquired immunity is the surface protein CD40. When combined with its receptor a costimulatory signal for interaction between antigen presenting cells and T-cells (Adam et al., 2003). Between innate and acquired immunity there is overlap. Both types of immunity interact, and in some cases utilize cell types to carry out the overall function of the immune system.

The Immune System's Role in Neoplasia and Metastasis Development

Cancer develops from the body's normal cells and transitions into cancer cells through deranged growth. There are seven common characteristics of the transition from normal cells to cancerous cells. This includes the ability of cancer cells to stimulate their own growth, resist the immune systems efforts to halt growth, cancer cells are not subject to normal apoptosis, they are able signal for new blood vessel development through angiogenesis, they multiply indefinitely, metastasize to other sites, and invade both acquired and innate immune system (Malik et al. 2014).

Once cancer cells have developed, they are able to form a primary tumor site known as a neoplasia. As the neoplasia develops its genetic makeup is changed to further aid in the development of more cancer cells and metastasis. With ongoing tumor growth, a normal inflammatory response is invoked, which signal for neutrophils, eosinophils, and monocytes to come to the tumor site. This creates an environment that is favorable for metastasis (Malik et al. 2014).

Research shows that there is a link between immune system dysfunction and the development of cancer metastasis. As pointed out by Critchley-Thorne et al. (2009),

innate immune dysfunction is a common defect in cancer patients. Specifically, the interferon signaling pathway is impaired, which, leads to lymphocyte dysfunction in cancer patients. To demonstrate this, Critchley-Thorne et al. (2009), took peripheral blood samples from patients who had breast cancer, gastrointestinal cancer, or melanoma. They then analyzed the samples from these patients and looked at the amount of interferon signaling gene expression (ISG) (Critchley-Thorne et al., 2009). The researchers found that the levels of the five major ISGs, were decreased when compared to healthy controls: STAT1, $p = 0.0381$; IFI44, $p = 0.0303$; IFIT, $p = 0.0480$; IFIT2, $p = 0.0177$; and MX1, $p = 0.019$ (Critchley-Thorne et al., 2009). This is indicative of lymphocyte dysfunction, which, leads to a decreased immune response in cancer patients. This decreased response allows for immune suppression and places the patient at a higher risk for infection. Chrichley-Thorne et al. (2009) also measured the response to IFN-α and IFN-γ stimulation in the peripheral blood lymphocyte samples from twenty-seven breast cancer patients (Critchley-Thorne et al., 2009). These patients had breast cancer stage two, three, and four. The researchers did the same for twelve patients with melanoma in stage three and four, as well as eleven patients with gastrointestinal cancer staged two, three, and four. These results were compared to twenty-eight aged matched healthy controls (Critchley-Thorne et al. 2009). The researchers found that changes in pSTAT1 induced by IFN-α was significantly reduced in T, B, and NK cells within all of the cancer types versus health controls ($p < 0.05$) (Critchley-Thorne et al., 2009). STAT1 plays a vital role in the formation of proteins necessary for the immune system to recognize and destroy viruses via the interferon alpha/beta pathway (US National Library of Medicine, 2019). The researchers then extrapolated that IFN signaling is reduced in

early stages of cancer and remains reduced in later stages (Critchley-Thorne et al., 2009). Thus, leaving cancer patients vulnerable to viral infections. Further research suggested by Critchley-Thorne et al. (2009), at the conclusion of this study, included enhancement of the human immune systems as a way to resist existing neoplasia and negate metastasis.

Since the work of researchers like Critchley-Thorne et al. (2009), immunotherapy has become a broad and ever-growing field. There are several types of immunotherapy treatments being developed as treatments for breast cancer. Vaccination as a way to get the immune system to recognize and attack cancer cells is one such example. For example, Delirezh, et al. (2016) sought to develop a vaccine to allow the immune system to recognize and thus attack the breast cancer cells. These researchers injected 4T1 mammary carcinoma cells into mice and waited until a palpable tumor developed. Mice were then randomly placed into either a control group where they received vaccines of phosphate buffered saline and a vaccination group, a vaccination group with 4T1 (4T1) only, or a vaccination group with 4T1 and naloxone (4T1+NLX). Naloxone has been used in cancer studies as an adjuvant to solutions and vaccinations (Bimonte et al., 2018). Naloxone has been shown to decrease the proliferation of breast cancer cells of the estrogen receptor-negative human breast carcinoma cells strain (Bimonte et al., 2018). Furthermore, Naloxone has also been shown to induce cancer cell apoptosis (Bimonte et al., 2018).

The vaccination groups were injected at regular intervals with heated 4T1 extract mixed with naloxone (Delirezh, et al., 2016), and a second ground that received 4T1 without any additive. Tumor growth was measured throughout the injection period. The amount of splenocyte and cytokine release was measured after euthanasia. Splenocytes

are white blood cells that come from the spleen. The reduction in splenocytes are indicative of a suppressed immune system (Guyton & Hall, 2011). Cytokines are peptides that are secreted by cells and function as signaling molecules. Examples of cytokines include interleukins and lymphokines (Guyton & Hall, 2011). The reduction in cytokines leads to less signaling and overall reduction in function of both innate and acquired immunity (Guyton & Hall, 2011).

Cytokine release IFN-γ production was upregulated in the heated 4T1+NLX group as compared to the control group ($p<0.05$) (Delirezh, et al., 2016). Overall tumor size was also decreased in the 4T1+NLX group ($p<0.05$). There was also more phagocyte production in the 4T1+NLX group when compared to the control group ($p<0.001$). Tumor size in the 4T1 group was similar in size to the control tumor mice. Splenocyte proliferation was higher in the 4T1+NLX group compared to the 4T1 mice. Overall findings indicate that vaccination utilizing heated 4T1 with naloxone increases the ability of the immune system to recognize breast cancer cells, increases the amount of phagocytes available to destroy the cancer cells, and limits overall tumor growth (Delirezh, et al., 2016).

Breast Cancer

According to the United States Center for Disease Control and Prevention, breast cancer is the most common type of cancer among women of all races (Centers for Disease Control, 2019). In the year 2016, there were 245,299 new cases of breast cancer in the United States (Centers for Disease Control, 2019). Forty-one thousand, four hundred eighty-seven women died of breast cancer in 2016. The risk of getting breast cancer among women of all races has not increased overall in the last decade (Centers for

Disease Control, 2019); However, it has increased significantly among African Americans and Asian Americans races. Risk factors for breast cancer are both modifiable and nonmodifiable. Modifiable risk factors that increase the risk of breast cancer include sedentary lifestyle, obesity, hormone replacement post-menopause and hormone birth control (Aryandono et al., 2017), reproductive history including not having a child or having a child over the age of 30, and alcohol intake (Centers for Disease Control, 2019) . Nonmodifiable risk factors include increased age, genetic mutations such as having the BRCA1 or BRCA2 gene, having dense breasts, family history of breast cancer (Aryandono et al., 2 017), and previous radiation therapy (Centers for Disease Control, 2019).

Early detection of breast cancer increases overall survival and usually discovered via mammography; however the lesion may be found by an individual during a breast self-exam (Norris, 2019). Diagnosis of breast cancer is done through mammography, ultrasonography, needle aspiration, and or excisional biopsy. Breast cancer often presents as a unilateral, solitary, firm, fixed, painless lesion. Usually the boarders are poorly defined (Norris, 2019).

Surgical resection of tumors is considered a definitive and first line treatment for solid neoplasms such as breast cancer (Ben-Eliyahu & Neeman, 2013). However, surgery is often associated with promotion of micrometastasis, which then allow for the development of new metastatic sites (Ben-Eliyahu & Neeman, 2013). According to the National Cancer Institute (2019), micrometastasis are small numbers of cancer cells that are released and spread away from the primary tumor site; however, the amount is too

small to be detected on any screening or diagnostic test. If left unchecked by the immune system, micrometastasis leads to additional tumor sites throughout the body.

Recenlty, Chang et al. (2019) identified a key enzyme involved with inhibition of the immune system in response to breast cancer. Specifically, the immune system's ability to upregulate the amount of CD8+ T cells available, as well as the amount of immune stimulatory myeloid subsets (Chang et al., 2019). Certain types of breast cancers can upregulate the enzyme calcium/calmodulin-dependent kinase (CaMKK2), which allows for the suppression of CD8+ and immune stimulatory myeloid subsets. Once CD8+ and immune stimulatory subsets are inhibited, neoplasia can successfully avoid recognition, and ultimately destruction, by the immune system (Chang et al., 2019). Researchers took breast cancer samples from willing participants and extracted cells. Cells were then injected into murine models and samples of the tumors were collected (Changet al., 2019). Results revealed that CaMKK2 was present at high levels within the breast cancer cells, and CD8+ T cells were suppressed (p <0.05). However, when the researchers suppressed CaMKK2 in breast cancer cells, CD8+ T cells were then detectable, and resulted in tumor growth inhibition (p <0.05) (Chang et al., 2019). This study demonstrates that by inhibiting the CaMKK2 pathway, CD8+ cells are available to aid in tumor suppression and limit overall tumor cell growth.

Surgical Procedures for Excision of Cancerous Breast Tumors.

Historically, radical mastectomies were the surgery of choice for breast cancer. This surgical technique is very invasive and involves the removal of the breast and underlying pectoral muscles. During this procedure the axillary lymph nodes are also

removed. This technique has been replaced with less invasive techniques (Golianu et al., 2018).

There are now two primary, minimally invasive, approaches to excision of cancerous breast tumors. One technique spares most breast tissue. The aim of this approach is to remove the tumor only. This approach is termed lumpectomy. The second approach is removal of the breast in its entirety. This is called mastectomy (Dave et al., 2010). Mastectomy is the technique of choice for more invasive breast cancer with extensive duct involvement or with a perceived high risk of metastasis. Mastectomy can also be done prophylactically for high risk patients. Both techniques can be accompanied by lymphatic mapping, sentinel node biopsy, and or axillary dissection (Golianu et al., 2018).

In a twenty year follow up to a randomized control trial, investigators found no difference in survival rates between radical mastectomy and less invasive surgical techniques (Cascinelli et al., 2002). From the years 1973 to 1980, 701 women with breast cancer tumors that measured more than 2 cm were randomly assigned to undergo either a radical mastectomy or less invasive quadrantectomy (Cascinelli et al., 2002). Both groups received radiotherapy to the ipsilateral breast tissue. There were 349 patients in the radical mastectomy group and 352 in the quadrantectomy group. After the year 1976 if patients in either group had positive axillary node involvement, they then received chemotherapy (Cascinelli et al., 2002). At the twenty year follow up, thirty women in the quadrantectomy group had tumor recurrence in the same breast while eight women had local recurrences in the radical mastectomy group, which is a statistically significant difference ($p < 0.001$) (Cascinelli et al., 2002). There was no significant difference

between the two groups in the rates of contralateral breast cancers, distant metastases, or secondary cancers.

At the 20 year follow up the rate of death from all causes was found to be 41.7 percent in the quadrantectomy group and 41.2 in the radical mastectomy group (Cascinelli et al., 2002). During that same time period, it was shown that there was more cancer recurrence and associated metastasis with less invasive techniques, such as lumpectomy. This is linked with the amount of micrometastasis at time of diagnosis and not with the surgical technique (Cascinelli et al., 2002). Overall surgery no matter what type, is associated with the acceleration and development of micrometastasis and the promotion of new metastasis.

The processes thought to be responsible for metastasis related to surgery is the suppression of acquired immune cell responses. Surgery involves the manipulation of the neoplasm, its surrounding vasculature, and lymphatic system (Ben-Eliyahu & Goldfarb,2007). During the perioperative period, natural killer cell suppression and upregulation of proangiogenic factors such as VEGF, allow for micrometastasis to not only evade recognition, and stop the metastatic cells from being phagocytized, but allow for easy invasion to other areas (Ben-Eliyahu & Goldfarb, 2007). Although the pathophysiology behind natural killer cell activity suppression after surgery is still not completely understood, it has been shown to be suppressed within hours of the surgery, and has been shown to last for several days postoperatively (Ben-Eliyahu & Goldfarb, 2007). There are several proposed mechanisms that could explain the decrease in NK cell cytotoxicity post-surgery. According to Lotzva et al. (1991), NK cell cytotoxic impairment is caused by a “toxic” effect. This is caused by the surge of catecholamines,

glucocorticoids, and prostaglandins from surgery. Together these substances have been shown to suppress NK cell activity (Lotzva et al., 1991). A study by Angka et al. (2017), linked the inflammatory response, specifically the increased amount of IL-6 production during both the acute proinflammatory phase and the prolonged anti-inflammatory phase, with NK cell suppression and cytotoxicity.

The deleterious effects associated with surgery are mediated through several mechanisms. This includes the surgical stress response that is mediated by neuroendocrine and metabolic responses (Buggy et al., 2006). These responses lead to a transient inhibition of the immune system, which allows for the cancer cells to further metastasize and develop new tumor sites (Buggy et al., 2006).

Anesthesia Plans for Breast Cancer Tumor Excision

Anesthetic plans are determined on an individual basis and are decided upon due to the patient's pathophysiologic conditions, physical limitations, adverse medication reactions, and creating optimal surgical conditions. However, some generalizations can be made. In the case of breast cancer tumor excision, the decision to use one technique over the other is based on many factors including anesthetic provider preference, surgeon preference, the patients' physiologic state, and type of procedure being performed (Nagelhout & Plaus, 2016). General anesthesia is always used, although the type of general anesthetic may vary. Sometimes providers may utilize regional techniques, such as paravertebral blocks, to provide more postoperative pain relief (Golianu et al., 2018).

General anesthesia: Volatile agent Sevoflurane. General anesthesia consists of insertion of an advanced airway, such as laryngeal mask airway or endotracheal tube (Nagelhout & Plaus, 2016). his allows the provider to ventilate the patient and administer

volatile anesthetic agents (Nagelhout & Plaus, 2016). Volatile agents allow for the patient to be placed in stage three of general anesthesia (Nagelhout & Plaus, 2016). In this stage patients will not respond to noxious stimuli such as a surgical incision (Nagelhout & Plaus, 2016). There are several volatile agents used in practice today to achieve this depth of anesthesia. One of the most commonly used agents is Sevoflurane (Nagelhout & Plaus, 2016).

Sevoflurane is a newer inhaled anesthetic that was discovered in the late 1960s and began to be commonly used in the 1990s. Advantages of sevoflurane include rapid uptake and elimination. It has good bronchodilating properties that make it appropriate for use in asthmatics and to lessen the risk of bronchospasm during induction, maintenance, and emergence phases of anesthesia. The cardiovascular effects are similar to that of an older volatile agent isoflurane. It provides good heart rate stability with slight reductions in cardiac output. Like all volatile agents, it provides dose dependent reductions in systemic vascular resistance and mean arteriolar pressures (Nagelhout & Plaus, 2016).

There are some disadvantages specific to sevoflurane. It is highly reactive with the desiccated carbon dioxide absorbent soda lime. When used with desiccated absorbents, sevoflurane has been linked with machine fires and patient injury. A second disadvantage is that it has been shown to cause renal failure in murine studies. This was attributed to Compound A formation when sevoflurane was administered with fresh gas flow rates less than two liters per minute (Nagelhout & Plaus, 2016).

All volatile anesthetic agents suppress all components of the immune system. This includes acquired and innate immune system components. The amount and which

specific cells are suppressed, depend on the agent used (Benzonana et al., 2011). Specifically, Sevoflurane has been shown to decrease the number of neutrophils, macrophages, T lymphocytes, and B lymphocytes (Dou et al., 2016). Sevoflurane has also been shown to reduce the cytotoxicity of NK cells (Dou et al., 2016).

A study done by Buggy et al. (2013), which utilized in vitro models, demonstrated increased breast cancer proliferation and metastasis with the use of Sevoflurane. Two types of breast cancer cells were utilized for this study, MCF7 ER+, which is estrogen receptor negative human breast adenocarcinoma, and MDA-MB-231 ER-, estrogen and progesterone receptor-positive human breast adenocarcinoma (Buggy et al., 2013). Both types of cells were incubated with or without Sevoflurane at concentrations of 1, 2, 3, and 4 mM for six hours. The researchers utilized cell proliferation migration and invasion assays to measure the effects of the Sevoflurane on the breast cancer cells. An independent t-test analysis compared for differences between the Sevoflurane and non-Sevoflurane groups. Sevoflurane increased proliferation of MCF7 cells by 50-60% (Buggy et al., 2013). Sevoflurane was also found to increase proliferation of MDA-MB-231 cells by 50-67% ($p<0.05$) (Buggy et al., 2013). Sevoflurane increased migration by 30-58% in the MCF7 ($p = 0.04$) and 30-230% in the MDA-MB-231 group (Buggy et al., 2013). Invasion ranged from 100-170% in MCF-7 ($p = 0.02$) and 28-72% in the MDA-MB-231 group, with statistical significance at the 4 mM concentration (Buggy et al., 2013). This study demonstrates that Sevoflurane inhalation anesthetic creates a proliferation of breast cancer cells, thus is not the ideal choice for breast cancer surgery.

Total intravenous anesthesia. Total Intravenous Anesthesia (TIVA) is the maintenance of anesthesia using intravenous medications only. No inhalation agents are

used for the maintenance phase of the anesthetic. The most common indication for TIVA is if the patient has a known history of malignant hyperthermia or has a risk for malignant hyperthermia. Some less common indications include long QT syndrome, surgery requiring neurophysiological monitoring, and Myesthenia Gravis and other neurological disorders to avoid neuromuscular blocking agents (Al-Rifai & Mulvey, 2016). Commonly propofol is used as the agent of choice for TIVA. It provides good hypnosis, amnesia, and has some level of antiemetic effect. Propofol can also be used in conjunction with the opioid Remifentanil to provide adequate pain management and synergistic sedation for the maintenance phase of the anesthetic (Nagelhout & Plaus, 2018). Propofol does not impair the function of NK cells like Sevoflurane does (Dilger, 2018). Propofol has also been shown to have better long-term survival rates when compared to volatile agents such as Sevoflurane (Jhanji et al., 2016).

In addition to the above listed benefits, propofol has been shown to aid in the infiltration of cancerous tumors with the body's own NK cells and T lymphocytes (Buggy et al., 2015). In a follow-up pilot study done by Buggy et al., (2015), ethics committee approval was given to contact patients currently involved in another breast cancer study. Thirty women who were already randomized into another clinical trial were contacted and consented to have their breast tissue reviewed and re-stained for immunocyte infiltration. Participants were randomized into two anesthetic groups: Propofol-paravertebral anesthesia (PPA, n=12) or general anesthesia with opioid analgesia (GA, n=16) (Buggy et al., 2015). The amount of infiltration was measured via the amount of CD4 (T Helper cells), CD8 (T suppressor cells), CD56 (NK cells) and CD68 (macrophages) cells that were present in the sample after staining (Buggy et al.,

2015). The normalized positive intensity values (median and interquartile range IRQ) showed that CD56 (NK cells) was lower in the GA group 121 versus the PPA group 136 ($p = 0.015$). The CD4 (T Helper cells) cell count was also lower in the GA group 10.9 (5.5-27.8) versus PPA 19.7 (14.4-83.5) ($p = 0.03$) (Buggy et al., 2015). This demonstrated that there is more infiltration by NK cells as well as T helper cell into breast cancer samples, as the overall number of NK cells and T helper cells present in the stained tissue was higher. If there are more NK cells present to mount an immune response against the cancer cells there will be less metastasis.

In murine models propofol has further been shown to suppress some NK activity but lead to less metastasis when compared to thiopental, ketamine, and halothane (Bar-Yosef, et al., 2003). In a study of 344 anesthetized rats, subjects were anesthetized for one hour with either: ketamine, thiopental, halothane, or propofol (Bar-Yosef, et al., 2003). The rats were then injected with breast cancer, specifically MADB106, tumor cells (Bar-Yosef, et al., 2003). At the twenty-four hour mark the amount of lung metastasis was counted. A second count of metastasis was made at the three-week mark. The researchers also counted the amount of circulating NK cells right after anesthesia. Propofol caused a 23.5% reduction in NK cells whereas thiopental had an NK reduction of 55.13%, which was the largest NK reduction among the selected agents (Bar-Yosef, et al., 2003). Ketamine demonstrated the highest amount of lung metastasis whereas propofol had the least amount (Bar-Yosef, et al., 2003).

Several studies have examined the connection between cancer, immunity, and metastasis. For example, according to Ah et al. (2016) propofol independently reduces cancer cell migration and leads to less metastasis. This led researchers in this retrospective study to examine if propofol based TIVA or sevoflurane anesthesia for modified mastectomy would lead to better five-year survival rates. Ah et al. (2016) analyzed data from 363 cases. Of these, 173 patients underwent modified radical mastectomy with TIVA and 152 underwent modified radical mastectomy with sevoflurane. The findings showed that there were no differences in survival between the two groups. However, the TIVA group had a significantly lower cancer recurrence rate (11.6%) versus the sevoflurane group (19.1%) ($p = 0.037$) (Ah et al., 2016). At the five-year mark, 9 of 173 (5.2%) patient deaths occurred in the Propofol group whereas 11 out of 153 (7.2%) patients in the Sevoflurane group had passed away (Ah et al., 2016).

Andreasson et al. (2014) also demonstrated that propofol was a better anesthetic choice for one-year survival for breast cancer patients than sevoflurane. In a retrospective case study, researchers examined surgical cases for patients undergoing a variety of surgical procedures for resection of cancer. Women who had undergone resection of breast cancer tumors were included, as well as patients who had undergone procedures for colon and rectal cancers. One thousand eight hundred and thirty-seven breast cancer patients were included within the study population. Although investigators found no overall difference in survival between sevoflurane or TIVA groups at the five-year mark, there were significant findings for the one-year mark. Specifically, the findings showed that breast cancer patients had a better survival rate at the one-year mark when TIVA had

been used versus sevoflurane (Andreasson et. al., 2014). Patients that had undergone breast cancer surgery with sevoflurane based anesthesia had a one-year survival confidence interval of 0.96, whereas the propofol based TIVA group had a confidence interval of 0.99 at the one-year mark (Andreasson et. al., 2014). The difference in survival between the two groups was a confidence interval of 0.03 (0.01-0.04) ($p < 0.001$) (Andreasson et. al., 2014). In addition, the researchers looked at all surgical survival rates combined, and found that propofol based TIVA had a better overall survival rate ($p = 0.004$) (Andreasson et. al., 2014).

The immune system is complex and its influence on the development of breast cancer and metastasis is even more so. Research has shown that when the immune system is unable to function in its normal capacity, breast cancer is able to develop and eventually metastasize. Several studies have shown that the type of general anesthesia used for the maintenance phase of breast cancer tumor excision, either volatile agent Sevoflurane or TIVA, can suppress the immune system and aid in development of metastasis. As anesthesia providers formulate an anesthetic plan for patients undergoing breast cancer tumor excision, immune system optimization should be a primary goal. Selection of a general anesthetic should limit the amount of immune response, which in turn could lead to better long-term survival.

Therefore, the purpose of this systematic review is to examine if Total Intravenous Anesthesia versus sevoflurane is more efficacious in limiting the amounts of immune cells released during the perioperative period in breast cancer patients. Relevant literature was explored to examine anesthetic choice and its effect on the immune system,

surgical advances impact on survival, and breast cancer survival rates with Sevoflurane and TIVA.

Next the theoretical framework used to guide this study is presented.

Theoretical Framework

A theoretical framework is utilized in research to serve as an organizational outline that pertains to a particular theory. The theoretical framework helps to serve insight into the topic of choice. It also provides strength to the research as well as gives reasoning as to why a particular topic requires further study.

The theoretical framework that guided this systematic review is the Preferred Reporting Items for a Systematic Reviews and Meta-Analyses (PRISMA). PRISMA is a 27-item checklist and a flow diagram. The diagram is a four-phase diagram (Altman et al., 2009). The included items are necessary for transparent reporting of a systematic review.

The PRISMA checklist is divided into seven sections. These sections include abstract, introduction, methods, results, discussion, and findings (Altman et al., 2009). Each section is used to compile a thorough review of each article (Altman et al, 2009).

The four-phase diagram is a graphic representation of the final articles used. It identifies the articles used, screening used, and eligibility determination. The diagrams, shown on page 27 and 28, also illustrate how many records were found and which databases were searched (Altman et al., 2009).

Next, the methods will be discussed.

Supplemental Table 2. PRISMA 2009 checklist for reporting of systematic reviews and meta-analyses.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	See title, page 1.
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	See abstract, page 2.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	See introduction, page 3.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	See introduction, page 3.
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	See methods, page 4.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	See methods, page 3.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	See methods, page 4.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See methods, page 3.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	See methods, page 4.
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	See methods, page 4.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	See methods, page 4.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	See supplemental table 1.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	See methods, page 4.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	See supplemental table 1.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	See methods, page 4.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	See figure 1.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	See table 1 and 2.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	See supplemental table 1.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	See table 1 and 2.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	See table 1 and 2.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	See results, page 8.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	See results, pages 8-9.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	See discussion, pages 9-10.
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	See discussion, pages 10-11.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	See discussion, page 11.
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	See discussion, page 11.

Figure 1. PRISMA Checklist

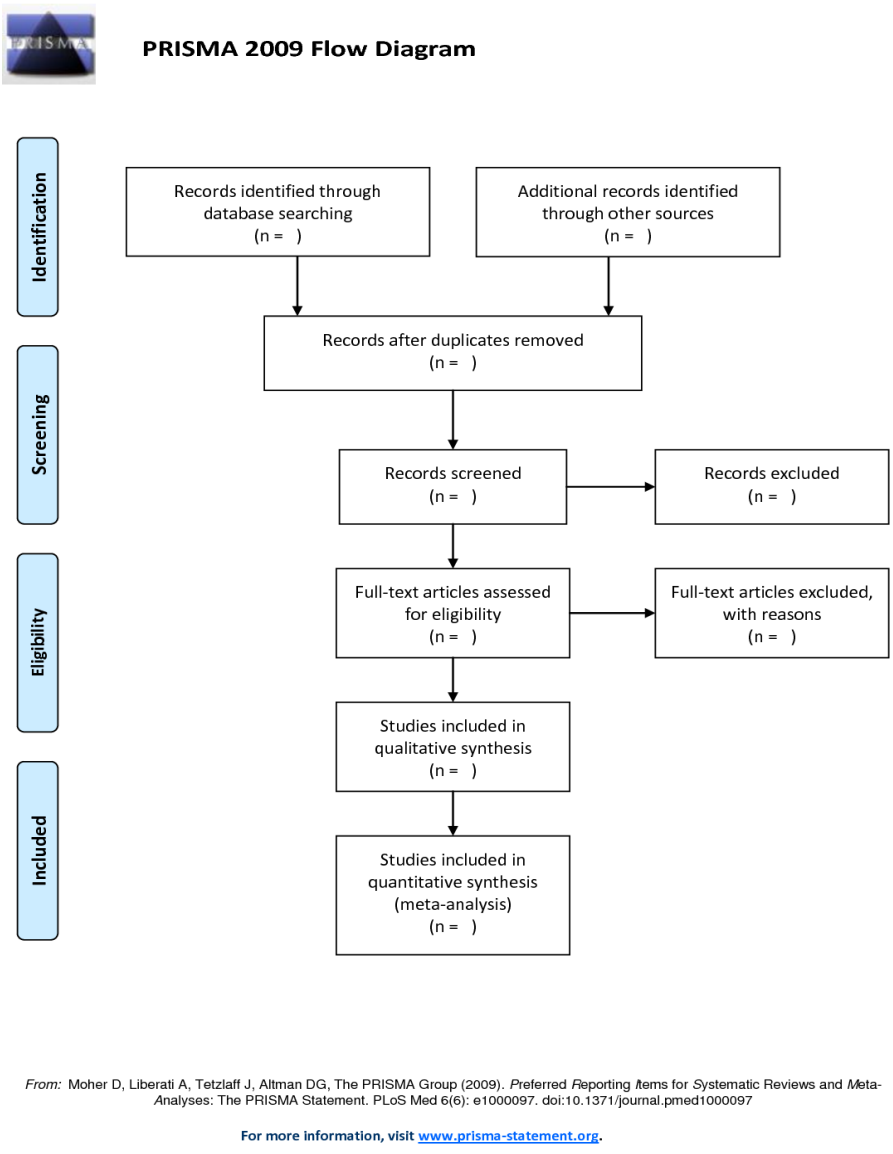


Figure 2. PRISMA Flow Diagram

Methods

Purpose

The purpose of this study is to examine if Total Intravenous Anesthesia versus sevoflurane is more efficacious in limiting the amounts of immune cells released during the perioperative period in breast cancer patients.

Design

The design of this study is a systematic review of the literature.

Search Strategy

Research studies were sought through data bases including Pubmed, CINHAL, and Medline. Search terms included were: Sevoflurane, TIVA, breast cancer surgery, mastectomy, immune response, and lumpectomy. Additional literature was sought using Google Scholar.

Inclusion/Exclusion Criteria

Inclusion criteria for studies reviewed were: (a) adult females age 20-80 (b) female patients undergoing surgical procedures for the excision of breast cancer tumors (c) randomized control trials that have compared TIVA to sevoflurane as the anesthetic during the maintenance portion of the procedure, and (d) quantitative measurement of amounts, as well as identification of types of cells measured. Studies that utilized supplemental pain control or nerve blocks for pain management were included. Studies were included regardless of induction agent used. Studies including males, children, and females over the age of 80 years old were excluded.

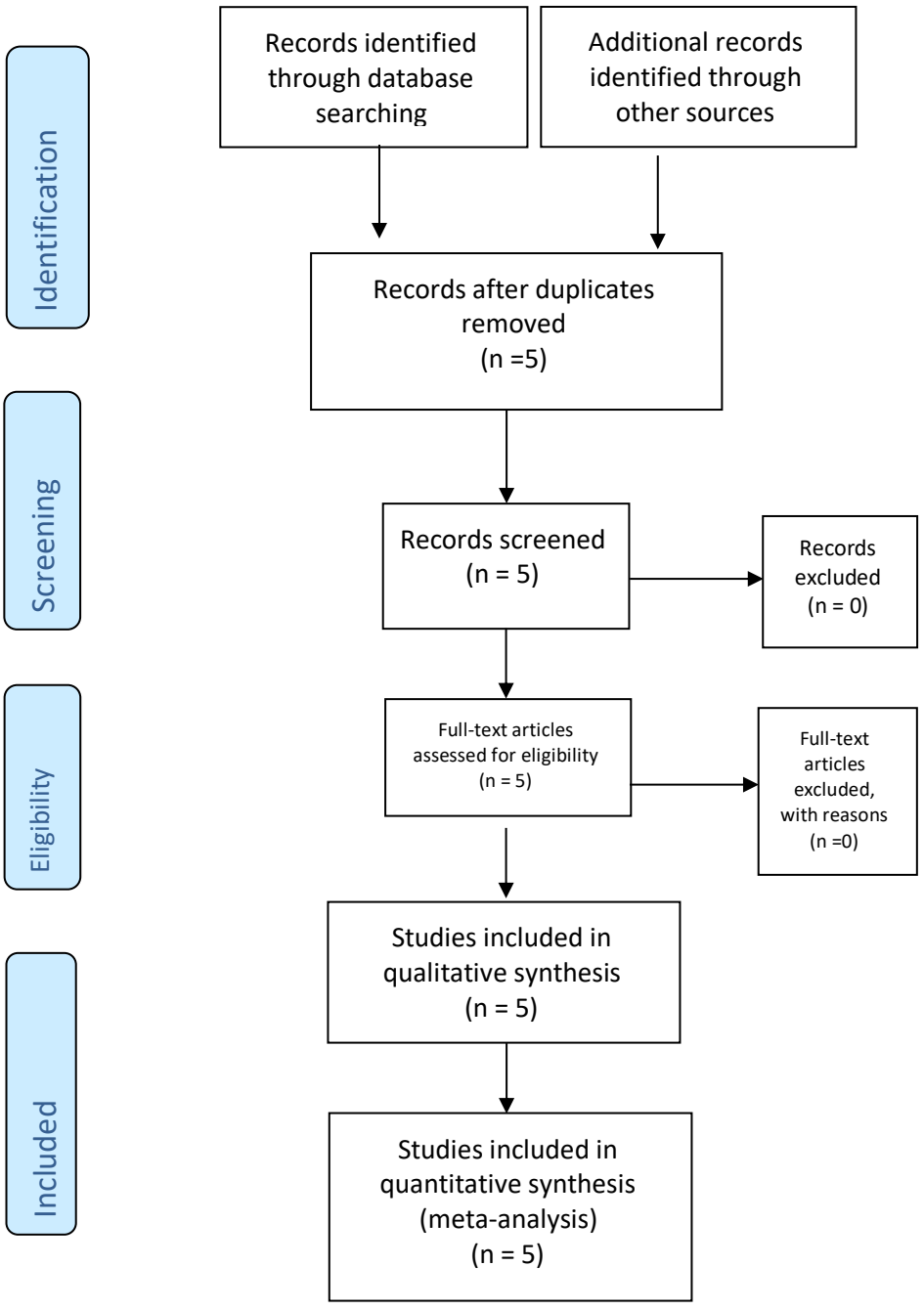
Data Collection

The study information collected included aim, design, site, sample, method, and outcomes. Outcome specific data sought included the inflammatory cell that was measured and patient outcomes related to amount of metastasis. The primary outcome variable that was collected is the amount of immune cell released in response to the specific type of anesthesia.

Critical Appraisal and Cross Study Analysis

The Critical Appraisal Skills Programme was used to appraise validity of the research studies analyzed. The CASP checklist is an 11question series used to determine if randomized control trials are appropriate to use in a systematic review. It is further divided into three sections. The first section is to review the validity of the study. There are five questions within the first section. The researcher answers the questions to help determine if the results of the study are valid. The second section is to review the results of the study. This section contains two questions. The researcher answers each question to determine what the results of the study are. The last section is the application of the study to the population at hand. There are three questions within this section. These questions help to establish how the results can be applied to practice (CASP, 2017). The checklist, shown on page 31, in its entirety provides a concise way to evaluate each systematic review individually.

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Results

The completed flow diagram, ash shown on page 31, is a visual demonstrating how the final five studies were chosen to implement in this systematic review. The initial search term “Sevoflurane” was used and resulted in 18,466 studies. Additional search terms including “Propofol” and “TIVA” narrowed the results to 285. Lastly, the terms “immune” and “breast cancer” were added and narrowed the results to 5 studies. There were no duplicate articles to exclude from this systematic review. After article screening, none were excluded, as all of the five studies met inclusion criteria previously identified. The remaining five articles were selected to complete this systematic review to determine if total intravenous anesthesia versus Sevoflurane is more efficacious in limiting the amounts of immune cells released during the perioperative period in breast cancer patients.

Each of the studies reviewed for this systematic review have an explanation of the results with the study findings clearly identified. Study specific data is shown in Appendix A (Tables A1-A5). Information obtained for these tables include the study design, purpose, location, sample size, and methods. Outcome data collection tables were created to summarize the results of those studies. The tables are included in Appendix B (Tables B1-B5). Specific findings include what types of immune cells were studied and amounts of cells released in identified time intervals. Critical appraisal data tables (Appendix C, Tables C1-C5) were used to assess the validity, reliability, and applicability of the studies included in this systematic review. Lastly, a cross-study analysis data table was used (Appendix D) comparing the results of each study.

Individual Studies

The single-center, randomized, parallel group study by Yan et al. (2018) (Appendix A, Table A-1) examined the effects of Propofol based TIVA and Sevoflurane anesthetic on proangiogenic factors and further evaluated for a correlation between proangiogenic factors released in occurrence free survival in breast cancer patients. A total of 83 patients who underwent breast cancer surgery, specifically modified radical mastectomy or breast conserving surgery, were divided into two groups. Group 1 (n=42) was the Propofol based TIVA group. These patients received Propofol and Remifentanil infusions for TIVA during the maintenance phase of anesthesia. Group 2 (n=41) was the Sevoflurane inhalation anesthetic group. These patients received Sevoflurane for the maintenance phase of anesthesia. Both group 1 and group 2 were induced with Fentanyl 2-3 μg/kg, Propofol 1-2 μg/kg, and paralyzed with Rocuronium 0.6 mg/kg. Fresh gas flows of 2L/min were maintained on both groups as well as an [exhaled] carbon dioxide level of 35-45 mmHg. Both groups had blood drawn at standardized times, specifically preoperatively and postoperatively at the 24-hour mark.

Outcomes of the study done by Yan et al. (2018) (Appendix B, Table B-1) showed that VEGF-C levels increased from 133 (80-205) to 140 (92-250) in group 1 (TIVA). There was a pre-post change value of 12 (-8-52) in this group. Group 2 had an increase in VEGF-C values from 105 (87-193) to 174 (111-281) and a pre-post change value of 3 (-3-47). The difference between groups' VEGF-C values were not statistically significant preoperatively (p=0.729) or postoperatively (p=0.177). The pre-post change value, however, was statistically significant (p=0.008) in both groups. When comparing

TGF-β levels in group 1 preoperatively to postoperatively, those levels decreased from 198 (100-304) to 176. There was a change value of 13 (-17-51) in the TIVA group. Group 2 experienced an increase in TGF-β levels when comparing preoperative values, 197 (131-318), to postoperative values, 211 (109-308). This group had a change value of 3 (-30 - 47). The levels of TGF-β were not statistically significant in the preoperative (p=0.721), postoperative (p=0.794), or pre-post changes (p=0.582), when comparing the two groups values. Group 1 had a recurrence free survival of 95% at the two-year mark. Group 2 had a recurrence free survival of 75% at the two-year mark. When comparing both groups, recurrence free survival was not statistically significant (p=0.221).

Utilizing the CASP questionnaire, (Appendix C, Table C-1), this study (Yan et al., 2018) has a clearly focused issue. All patients involved were randomized and both groups were similar at the start of the trial. Aside from the clinical intervention both groups were treated equally throughout the study. In addition, the healthcare members involved in measuring of the blood samples for the study were blinded as to which intervention the patient received. The results of this study can be applied to adult females undergoing breast cancer tumor removal that require general anesthesia. There are several limitations to this study. First, Propofol was used for induction for both groups. Propofol would have dissipated within 10-15 minutes after administration, but it is unclear if this affected the results of this study. Secondly, the number of patients enrolled in this study was small (n=83). Finally, this study was carried out in a single center.

The tri-center, prospective study by Ito et al. (2017) (Appendix A, Table A-2) looked at the effect of anesthetic technique (Propofol based TIVA versus Sevoflurane) on the immune response in patients undergoing breast cancer surgery in a day center or

hospital. A total of 37 patients who underwent breast cancer surgery, specifically, partial resection of the breast, sentinel lymph node biopsy with axillary lymph node dissection, or total mastectomy, were divided into two groups. Group 1 (n=21) was the Propofol based TIVA day center group. These patients received Propofol, lidocaine, and Pethidine for TIVA during the maintenance phase of anesthesia. Group 2 (n=16), was the Sevoflurane with Propofol or Propofol with opioid TIVA hospitalized group. Seven patients (n=7) received TIVA of Propofol (1-3µg/mL with Remifentanil (0.25 µg/kg/min) for maintenance while Propofol (3µg/mL) and Fentanyl (1-2µg/kg) were administered at induction. Four patients (n=4) received TIVA with Propofol (3µg/mL) for maintenance with Fentanyl (1-2µg/kg) and Propofol (2µg/kg) given at induction. Four patients (n=4) received Sevoflurane inhalation anesthetic (1.0-5.0%) and Remifentanil (0.25 µg/kg/min) drip for maintenance with Propofol (2µg/kg) and Fentanyl (1-2 µg/kg) given at induction. One patient (n=1) was maintained with Sevoflurane (1.0-5.0%) and given Propofol (3µg/mL) and Fentanyl (1-2 µg/kg) at induction. All patients in the hospitalized group were given Rocuronium (0.6 mg/kg) for paralysis and ventilated with a mixture of 1:2-3 O_2 and air. Both groups had blood drawn at standardized times, specifically, preoperatively, and postoperatively at the 24-hour mark.

Outcomes of the study done by Ito et al. (2017) (Appendix B, Table B-2) shows the median change values of NK Cell activity, CD4/8 T Cell Ratio, and IL-6 levels in the preoperative, postoperative, and 24-hours postoperatively. In Group 1 (day surgery TIVA group) median NK Cell activity preoperatively was 30.5± 9.2 and then fell to 29.0± 9.0. At the 24-hour mark the median NK Cell level rose to 32.0± 7.5. In Group 2 (hospitalized TIVA or Sevoflurane with opioid group) median NK cell activity was 24.5± 13.8. This

value rose to 31.0± 12.3 in the postoperative period and then fell to 25.0± 9.5 at the 24-hour postoperative mark. In group 1 the CD4/8 T Cell Ratio median value rose steadily throughout all three time periods. Values started at 1.31± 0.32, increased to 1.53± 0.64, and rose to 1.67± 0.34 by the 24-hour postoperative time period. In Group 2 CD4/8 T Cell Ratio median values started at 1.63± 0.55, decreased to 1.23± 0.16, and then increased almost to baseline with a median value of 1.61± 0.68. In group 1 IL-6 median values started at 1.1± 0.5, fell to 1.0± 0.65, and then increased to 5.4± 1.35 in the 24-hour postoperative time frame. Group 2 showed an increasing trend of median IL-6 values across all three time periods. Initially median values were measured at 2.0± 1.94. In the postoperative period those values increased from 3.9± 2.95 postoperatively to 15.3± 7.15 in the 24-hour postoperative period. There was no statistical validity testing done with these values.

Utilizing the CASP questionnaire, (Appendix C, Table C-2), this study (Ito et al., 2017) has a clearly focused issue, patients were not randomized, both groups were similar at the start of the trial, and aside from the clinical intervention both groups were treated equally throughout the study. The healthcare members involved were not blinded to the intervention that the patient received. The results of this study might be applied to adult females undergoing breast cancer tumor removal that require general anesthesia. There are several limitations to this study. First, propofol was used for induction for both groups. Propofol would have dissipated within 10-15 minutes after administration, but it is unclear if this could have affected the results of this study. Secondly, the number of patients enrolled in this study is small (n=37). Third, this study did not clearly separate the two methods of delivery of anesthesia. Patients were grouped according to the setting

in which they received care, either hospitalized or a day surgery center, and not by the medication they received for maintenance of anesthesia.

The single center, randomized, retrospective analysis of an ongoing randomized clinical trial study by Buggy et al. (2018) (Appendix A, Table A-3) sought to determine if the inflammatory response would be less in breast cancer patients who received propofol based TIVA than those who received sevoflurane/ opioid based anesthesia for removal of cancerous breast tumors. The researchers measured the amounts of neutrophil-lymphocyte ratio, white blood cell count, platelet count, and platelet-lymphocyte ratio. A total of 116 patients who underwent unilateral mastectomy, bilateral mastectomy, and lumpectomy with axillary node dissection that were enrolled in another ongoing randomized clinical trial were enrolled and divided into two groups. Group 1 (n=59) received propofol TIVA with a paravertebral nerve block. The paravertebral block was given as a one-time injection in the T1-T5 interspaces or an injection with thoracic epidural catheter placement, in the T2-T4 interspace, for continued postoperative pain management. Those that received an epidural catheter were administered a test dose of 1.5% Lidocaine and 1:200,000 epinephrine and then followed with either bupivacaine 0.5% or ropivacaine 0.5%. Those that were given multilevel injections were administered 5mL of 0.75% bupivacaine. Postoperative pain was managed with either the paravertebral block or non-steroidal anti-inflammatory drugs (NSAID's), morphine for intractable pain, and transitioned onto NSAID's and paracetamol by the 24-hour postoperative mark. Group 2 (n=57) had sevoflurane with an opioid administered as the chosen anesthetic. For this group, anesthesia was induced using fentanyl 2-4 μg/kg and propofol 1-3 mg/kg. Sevoflurane and fentanyl were given to maintain heart rate and

blood pressure within 20% of preoperative values. Morphine 0.1mg/kg was administered at the end of the surgery. Postoperative pain was managed with morphine or similar long acting opioid with a transition to paracetamol and NSAID by the 24-hour mark. Both groups had blood drawn at standardized times, specifically, preoperatively, and postoperatively.

Outcomes of the study done by Buggy et al. (2018) (Appendix B, Table B-3) shows the amounts of white blood cells, neutrophils, lymphocytes, platelets, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, as well as the change in the neutrophil-lymphocyte ratio in the preoperative and postoperative period. In the preoperative period group 1 median white blood cell level was 7.4, while group 2 had a median white blood cell level of 7.2. When comparing these two median values there was no statistically significant difference. In group 1, the median neutrophil count was 4.7 whereas the median value for group 2 was 4.6 in the preoperative period. There was no statistically significant difference between the groups. In the preoperative period the median lymphocyte count was 2.0, while group 2 had a median value of 1.9. There was no statistically significant difference between the groups. Median levels of platelets in the preoperative period for group 1 was 292 and 265 for group 1. There was no statistically significant difference between these groups. The neutrophil-lymphocyte ratio median value in group 1 was 3.0 and 4.0 for group 2 and was not statistically significant different. The platelet-lymphocyte ratio median value was 142 for group 1 in the preoperative period, and was 148 for group 2, with no significant difference.

In the postoperative period, group 1 and group 2 had a white blood cell count median value of 9.0. In the postoperative period, group 1 had a neutrophil count median

value of 6.4, whereas group 2 had a median value of 6.5. Group 1 had a median lymphocyte count of 1.8 and group 2 had a median lymphocyte count of 1.7. In the postoperative period group 1 had a median platelet value of 268. In the same time period, group 2 had a median platelet count of 237. The median neutrophil-lymphocyte ratio was significantly different (p=0.001*)* between the two groups (group 1: 3.0 versus group 2: 4.0). Similarly, the change in median neutrophil-lymphocyte count from the preoperative time period to the postoperative time period was also significant (*p*=0.001), with group 1 at 30% and group 2 at 82%. Finally, the median platelet-lymphocyte count in the postoperative period was 148 in group 1 and group 2 (Buggy et al., 2018).

Utilizing the CASP questionnaire, (Appendix C, Table C-3), this study Buggy et al. (2018) has a clearly focused issue. Patients were randomized and both groups were similar at the start of the trial. Aside from the clinical intervention, both groups were treated equally throughout the study. Whether the healthcare team was blinded to the treatment was not clear. The results of this study may be applied to adult females undergoing breast cancer tumor removal that require general anesthesia. There are several limitations to this study. First, propofol was used for induction for the sevoflurane group (group 2). Propofol would have dissipated within 10-15 minutes after administration, but it is unclear if this could have affected the results of this study. Secondly, blood samples postoperatively were taken at different times. All patients had all blood samples taken within 72 hours. However, when within the 72 hours the blood samples were taken varied.

The single-center, randomized, control trial by Oh et al. (2018) (Appendix A, Table A-4) compared the changes in amounts of cluster differentiation of regulatory T

cells in patients receiving propofol based TIVA or sevoflurane for breast cancer surgery. The researcher specifically measured the amounts of cluster differentiation enzyme 39 (CD39) and cluster differentiation enzyme 73(CD73) on regulatory T cells as well as the median neutrophil-lymphocyte ratio. A total of 201 women who underwent breast cancer surgery were divided into two groups. Group 1 (n=99) was the propofol based TIVA group. This group received propofol TIVA with a target concentration of 40 μg/mL using a TCI device. Group 2 (n=102) was the sevoflurane group. This group received thoipental5mg/kg for induction. Maintenance anesthesia was achieved with sevoflurane inhalation anesthetic with a Bispectral Index (BIS) monitoring goal of 40-60 with remifentanil drip at a goal concentration of 5.0ng/mL. Both groups received lidocaine 0.5mg/kg, rocuronium 0.6 mg/kg, ketorolac 0.5mg/kg, 0.03mg/kg neostigmine, and 0.008mg/kg glycopyrrolate were given to both groups. Mean arterial pressure was maintained at 20% of baseline for both groups. Both groups had blood drawn at standardized times, specifically, preoperatively, postoperatively by the 1-hour mark, and again at the 24-hour mark.

Outcomes of the study done by Oh et al. (2018) (Appendix B, Table B-4) showed that expression of CD39 decreased overall in group 1 with values in the preoperative time period of 17.1%, 16.7%± 7.6% in the first hour postoperative, and 16.9% in the 24-hours postoperatively. CD39 was expressed 17.6% in the preoperative period, 16.5%± 7.9% in the first hour postoperatively, and returned to baseline (17.6%) within 24-hours postoperatively in group 2. Frequency of CD73 expression in group 1 was 19.4% in the preoperative period, 18.5% in the first hour postoperatively, and 19.2% in the 24-hours postoperatively. In group 2 frequency of CD73 expression was shown to increase across

all three time intervals. The preoperative value was 19.0%, with an increase in expression to 19.2%, and finally 19.6% by the 24-hour time interval. Although there was an increase in value, this was not statistically significant (*p=0.658*). In group 1 the neutrophil-lymphocyte ratio increased from 1.55 in the preoperative time period to 1.62 in the first hour postoperatively. The neutrophil-lymphocyte ratio was not measured at the 24-hour postoperative mark. In group 2 the neutrophil-lymphocyte ratio decreased from 1.76 preoperatively to 1.68 at the 1-hour postoperative mark.

Utilizing the CASP questionnaire, (Appendix C, Table C-4), this study by Oh et al. (2018) has a clearly focused issue. All patients involved were randomized. Both groups were similar at the start of the trial and aside from the clinical intervention both groups were treated equally throughout the study. The healthcare members involved in measuring the blood samples for the study were blinded as to which intervention the patient received. The results of this study can be applied to adult females undergoing breast cancer tumor removal that require general anesthesia. There are several limitations to this study. First, opioids and ketorolac that were used could potentially mask the pure effect of sevoflurane or propofol TIVA on the values measured. Secondly, the use of immune markers, cluster differentiation 39 and 73, have not been proven to be a contributor to poor prognosis in humans as it has in animal studies (Antonioli et al., 2013). Finally, this study was carried out in a single center.

The single-center, randomized, double blind control trial by Kim et al. (2018) (Appendix A, Table A-5) sought to identify the effect of propofol TIVA versus sevoflurane on natural killer cells, cytotoxic T cells, IL-6 levels,IL-10, tumor necrosis factor-α (TNF-α), and apoptosis rates in patients undergoing surgery for breast cancer. A

total of 44 women who underwent breast cancer surgery were divided into two groups. Group 1 (n=23) was the propofol based TIVA group. This group received propofol TIVA with a target concentration of 40 μg/mL using a TCI device. Group 2 (n=21) was the sevoflurane group. This group received thoipental 5mg/kg for induction. Maintenance anesthesia was achieved with sevoflurane inhalation anesthetic with a Bispectral Index (BIS) monitoring goal of 40-60 with remifentanil drip at a goal concentration of 5.0ng/mL. Both groups received rocuronium 0.6 mg/kg, ketorolac 0.5mg/kg, 0.03mg/kg neostigmine, and 0.008mg/kg glycopyrrolate. Mean arterial pressure was maintained at 20% of baseline or greater than 60mmHg for both groups. Both groups had blood drawn at standardized times, specifically, preoperatively, postoperatively by the 1-hour mark, and again at the 24-hour mark.

Outcomes of the study done by Kim et al., (2018) (Appendix B, Table B-5) showed that in group 1 median TNF-α decreased initially but rose overall with values in the preoperative time interval of 413 (390-470), 390 (390-430) at the one hour postoperative time interval, and 420 (390-430) by the 24-hour time interval. In group 2 TNF-α levels followed the same pattern. Median values in the preoperative time interval were 404± 42, 400 (370-455) by the 1-hour postoperative mark, and then 417± 25 in the 24-hour postoperative time frame. When comparing values of TNF-α in the preoperative period between group 1 and group 2 there was no statistical significance (p=0.175). Furthermore, there was no statistical significance when comparing TNF-α values between group 1 and group 2 in either postoperative time period with values of p=0.953 at the 1-hour mark and p=0.958 at the 24-hour mark. Median levels of IL-6 in the preoperative time period were 90 for both groups 1 and 2. This was not statistically

significant with a value of *p=0.524*. By the one-hour postoperative mark, group 1 showed an increase in levels of IL-6 with median levels measuring 100 (90-100), while group 2 values remained the same at 90 (90-100). By the 24-hour postoperative mark, Il-6 levels were 90 (90-100) for both groups. Median levels of Il-10 fell overall in group 1. In the preoperative time period median values of Il-10 were 490 (450-550). In the 1-hour postoperative time period median values remained the same, 490 (440-550). By the 24-hour time frame the median IL-10 values fell to 470 (440-500) in group 1. In group 2 median levels of IL-10 were 470 (445-525) preoperatively, 450 (435-520) at the 1-hour postoperative mark, and 470 (440-500) by the 24-hour postoperative mark. When comparing median values of IL-10 from group 1 to group 2, none of the values proved to be statistically significant with values of p=0.430, p=0.340, and p=960.

Utilizing the CASP questionnaire, (Appendix C, Table C-4), this study by Kim et al., (2018) has a clearly focused issue. All patients involved were randomized and both groups were similar at the start of the trial. Aside from the clinical intervention both groups were treated equally throughout the study. The healthcare members involved in measuring of the blood samples for the study were double "blind" as to which intervention the patient received. The results of this study can be applied to adult females undergoing surgery to remove tumors caused by breast cancer. There are several limitations to this study. First, opioids and ketorolac that were used could potentially mask the pure effect of sevoflurane or propofol TIVA on the values measured. Secondly, there were very few women enrolled in the study (n=44). Lastly, this study was conducted at a single center.

Next, the summary and conclusions will be presented.

Summary and Conclusions

Metastasis of cancerous cells, specifically breast cancer cells, has been shown to increase chances of mortality. According to the National Cancer Institute (2018) breast cancer survival was about 90% overall. Patients with distant metastasis had a survival rate of 27% and those with regional metastasis had an 85% survival rate. This shows that the more metastasis to distant areas, the lower the chance of survival of the patient (American Cancer Society, 2019). It is theorized that surgery can increase the amount of metastasis (Simmons et al., 2017). Therefore, limiting the amount of metastasis caused from breast cancer surgery would increase chances of survival.

Propofol is a phenol derivative that has been shown have several benefits that may aid in limiting immune dysfunction in breast cancer patients related to surgery. Propofol has been shown to limit NK dysfunction (Dilger, 2018) and aid in infiltration of the cancer cells by the immune system's own NK cells and T lymphocytes (Buggy et al., 2015). In addition, propofol has also been shown to have better long-term survival rates when compared to volatile agents such as sevoflurane (Jhanji et al., 2016). Sevoflurane, a volatile inhalation anesthetic, has been shown to have a higher cancer recurrence rates in breast cancer patients (Lee et al., 2016). When comparing sevoflurane to propofol base TIVA, patients who received sevoflurane had a lower survival rate at the one-year mark (Andreasson et. al., 2014).

The purpose of this systematic review was to examine if Total Intravenous Anesthesia versus Sevoflurane is more efficacious in limiting the amounts of immune cells released during the perioperative period in breast cancer patients. A comprehensive literature review was completed using Pubmed, CINHAL, and Medline. This literature review focused on immunity, the immune system's role in neoplasia and metastasis,

breast cancer, surgical approaches for breast cancer, and both propofol and sevoflurane's effect on immunity involving breast cancer surgery. A theoretical framework was chosen to aid in the identification of eligible studies based on specific inclusion criteria. PRISMA was the theoretical framework chosen. It is a 27-item checklist and four-phase flowchart (Altman, et al., 2009).

Individual study analysis was completed on the final five studies meeting criteria. Study specific data tables were created outlining key information from each study. Data outcome tables were created to determine the efficacy of propofol based TIVA and sevoflurane on limiting the amounts of immune cells released during the perioperative period in breast cancer patients. Next, critical appraisal of individual RCT's was performed utilizing the Critical Appraisal Skills Programme (CASP) checklist. Last, a cross study analysis table was created to compare the types of immune cells released during the perioperative period.

There were several limitations noted when completing this systematic review. Some studies were not a randomized control study by design. Specifically, one study was a retrospective study of an ongoing randomized control trial and two studies were prospective control trials. The other two studies were randomized control trials. Secondly, two of the studies were not blinded. A third limitation is lack of consistence in which immune mediator was measured. Each study measured different immune cells and immune mediators; therefore there is a lack of congruency in results for comparison. Lastly, each study took blood samples at different times. This lack of consistency in time intervals for blood draws makes it difficult to draw definitive conclusions.

The findings of this systematic review determined that propofol based TIVA increases recurrence free survival, however there is negligible differences in the immune response between propofol based TIVA and sevoflurane inhalation anesthetic for women undergoing surgery for breast cancer tumor excision.

Next, the recommendations and implications for practice will be presented.

When weighing options in treatment for breast cancer, in many cases, the benefits of surgery outweigh the risks. Once the decision has been made to proceed with surgery, options for surgical approach are planned with the patient and surgeon in collaboration to choose the safest and most effective option. On the day of surgery, the anesthesia provider will meet the patient, assess them, and create an individualized anesthetic plan (Nagelhout & Plaus, 2018). The anesthesia provider will consider the patient's comorbidities, airway anatomy, length and type of surgery, and postoperative pain management when selecting an anesthetic plan (Nagelhout & Plaus, 2018). However, with patients undergoing surgery for breast cancer, the anesthesia provider should also individualize a plan that will increase the patient's chances of survival from breast cancer.

It is paramount that as anesthesia providers we always plan with the end in mind. In this case, the end should not be limited to the patients discharge from the recovery room. The end goal should be to increase chance of survival for the patient. Propofol has been shown to limit the amount of NK cell suppression in murine models (Bar-Yosef et al., 2003) and may increase the survival rate of patients undergoing breast cancer surgery at the two-year mark (Yan et al., 2018). However, as demonstrated in this systematic review, propofol may not have a noticeable effect on other immune mediators such as IL-6, IL-10, neutrophils, and platelet levels. Sevoflurane has been shown to elicit an immune response, but its effects may not be significant. Continued research is needed in this area to determine which anesthetic choice will lead to better patient outcomes. In addition,

anesthesia providers should continue to be educated in immunology and anesthetic impact on breast cancer patients.

The overall recommendation from this systematic review is that anesthesia providers should continue to individualize an anesthetic plan that places the patient's safety, comfort, and surgical success first. This systematic review has demonstrated that there is not a clear choice as to whether propofol based TIVA or sevoflurane will increase survivability and limit the immune response in this patient population. More research should be done in this area to identify if one method of anesthesia is superior to the other. Until such results are available, anesthesia providers should maximize survivability by limiting the surgical stress response in a way that also accounts for patient safety, pain management, and surgical success in breast cancer patients undergoing surgery for tumor removal.

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Appendix A

Table A-1

Study Specific Data

Sun, L., Wang, B.N., Yan, T., Zhang, G.H., & Zheng, H. (2018). Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: a prospective, randomized and controlled study. *BMC Anesthesiology*, *18*(1), N.P.AG. https://doi-org.ric.idm.oclc.org/10.1186/s12871-018-0588-3					
AIM/PURPOSE 1.Research to discover what effect Propofol based TIVA and Sevoflurane anesthetic techniques have on proangiogenic factors. 2. How the amount of the proangiogenic factors released may have a correlation with recurrence-free survival and overall survival rates in patients undergoing breast cancer resection surgery.	DESIGN Single center, controlled, parallel-group clinical trial, with randomization. Group 1-Propofol remifentanil-based TIV A Group 2-Sevoflurane inhalation anesthetic	SITE Cancer Hospital of Chinese Academy of Medical Sciences	SAMPLE 90 patients were assed for eligibility; 7 were excluded for a total of 83 included in the study. All patients underwent a modified radical mastectomy (MRM) or breast conserving surgery (BCS). Group 1-(n=42) Propofol/remifentanil Group 2-(n=41) Sevoflurane	METHODS Patients were randomized into the two groups. Group 1- Propofol drip3-6mg/kg/h and Remifentanil 0.1-0.2μg/kg/min Group 2-1.5-2% Sevoflurane with BIS values of 40-60.	PROCEDURES Group 1 and 2 were induced with Fentanyl 2-3μg/kg, Propofol 1-2mg/kg, and Rocuronium 0.6 mg/kg. LMA inserted, hemodynamics monitored, carbon dioxide maintained 35-45 mmHg, and a fresh gas flow of 2L/min oxygen. Fentanyl bolus' given intraoperatively as needed in both groups. NSAIDS given for pain management. Group 1-Propofol and Remifentanil drips for maintenance phase. Group 2-Sevoflurane for maintenance phase.

Appendix A

Table A-2
Study Specific Data

Ito, M., Kadoya, T., Funaoka, Y.,Kawai, A., Kim, R., Wakisaka, M.,Y., Ohtani, S., & Okada, M. (2017). Differences in immune response to anesthetics used for day surgery versus hospitalization surgery for breast cancer patients. *Clinical & Translational Medicine*, *6*(1), 1–8. Doi: 10.1186/s40169-017-0163-4 https://doi-org.ric.idm.oclc.org/10.1186/s40169-017-0163-4					
AIM/PURPOSE To discover what effect anesthetic technique used (TIVA versus Sevoflurane inhalation anesthetic) has on the immune response in patients undergoing breast cancer surgery in a day center versus hospitalization.	DESIGN Tri-center, prospective study. Group 1-Day surgery, Lidocaine/Propofol/Pethidine (TIVA) Group 2-Hospitalized, Sevoflurane/Propofol, systemic-opioid-based	SITE Day center: Hiroshima Mark Clinic Hospitalization: Hiroshima City Hospital or Hiroshima University Hospital	SAMPLE Thirty-seven patients who underwent partial resection of the breast (Bp), sentinel lymph node biopsy (SNB), (Bp) with axillar lymph node dissection (Ax), and a total mastectomy with Ax. Group 1-(n=21) Day surgery, lidocaine, Propofol, Pethidine (TIVA) Group 2-(n=16) Hospitalized Sevoflurane/Propofol, or Propofol systemic-opioid-based anesthesia (TIVA)	METHODS Patients were placed into groups based on hospital preference, and thus the anesthetic technique that coordinated with the chosen site. Blood levels were taken before, after, and 24 hours after surgery. **Group 1**- induction with 1mg.kg Propofol and 35mg Pethidine. Maintenance was achieved via Propofol TIVA 6-8mg/kg/h and 50-100mg of 0.5% Lidocaine for localization of the area. **Group 2**- Selection of technique was at the discretion of the anesthesiologist. Some patients (n=4) received Propofol and Fentanyl for induction, Sevoflurane gas and Remifentanil drip for maintenance. Some (n=7) received Propofol and Fentanyl for induction, Remifentanil/Fentanyl (TCI) TIVA for maintenance. Some patients(n=4) received Propofol and Fentanyl induction, Propofol and Fentanyl (TCI) TIVA for maintenance. Only one patient received Propofol and Fentanyl at induction and Sevoflurane for maintenance.	PROCEDURES Immune response was evaluated using the blood samples. Specifically measured was NK cell activity, CD4/8 T cell ratios, and levels of cytokines, IL-6 and IL-10

Appendix A

Table A-3
Study Specific Data

Buggy, D. J, Burns, D., Ní Eochagáin, A., Riedel, B., & Sessler, D. I. (2018). The effect of anaesthetic technique during primary breast cancer surgery on neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and return to intended oncological therapy. *Anaesthesia*, 73(5), 603–611. https://doi-org.ric.idm.oclc.org/10.1111/anae.14207					
AIM/PURPOSE	DESIGN	SITE	SAMPLE	METHODS	PROCEDURES
To determine if the inflammatory response would be less in breast cancer patients who received Propofol (TIVA) and paravertebral block versus Sevoflurane-opioid anesthesia for breast cancer surgery. Specifically measured was the neutrophil-lymphocyte ratio, white cell count, neutrophil count, platelet count, and platelet-lymphocyte ratio.	Single center, retrospective analysis of an ongoing randomized control trial Group 1-Propofol (TIVA)/paravertebral group Group 2-Sevoflurane/opioid	Mater University Hospital	116 patients who underwent unilateral mastectomy, bilateral mastectomy, lumpectomy with axillary node clearance. Group 1-(n=59) Propofol (TIVA)/paravertebral group Group 2-(n=57) Sevoflurane/opioid group	Patients were randomized into the two groups. Group 1- Paravertebral block with catheter placement, 10-20mL dose of 0.5% Bupivicaine or 0.5% ropivacaine with Epinephrine, at the end of the surgery 6-10mL of either solution were titrated in, Propofol (TIVA) 60-90μg/kg/min Group 2-induction with 1-3 μg/kg Fentanyl, 2-4mg/kg Propofol, maintenance using Sevoflurane, Morphine 0.1mg/kg given at the end of surgery.	Patients were randomized into either anesthetic group. Charts were reviewed and level of neutrophil-lymphocyte ratio was noted. These levels were taken before and after surgery.

Appendix A

Table A-4

Study Specific Data

Kim, S.H., Lee, J.Y., Lee., S.H., Oh, C.S., Park, H.J., Piao, L., H., Seo, E.H., & Yoon, T.G. (2018b). Effect of Equipotent Doses of Propofol versus Sevoflurane Anesthesia on Regulatory T Cells after Breast Cancer Surgery. Anesthesiology, 129(5), 921–931. https://doi-org.ric.idm.oclc.org/10.1097/ALN.0000000000002382					
AIM/PURPOSE The purpose of the study was to compare the amount of changes in cluster differentiation on regulatory T cells in patients receiving Propofol based TIVA and Sevoflurane for breast cancer surgery. Specifically, the researchers compared cluster differentiation of enzyme 39 and 73 on regulatory T cells. Amount of NK cells, cytotoxic T cells, cytokines, and neutrophil-to-lymphocyte ratio were also measured.	DESIGN Single center, randomized control trial. Group 1-Propofol (TIVA) Group 2-Sevoflurane	SITE Konkuk Universiry Medical Center, Korea	SAMPLE 201 women undergoing surgery for breast cancer. Group 1- (n=99) Propofol TIVA group Group 2-(n=102) Sevoflurane group	METHODS Patients were randomized into the two groups. Blood samples were obtained prior to induction and 24 hours postoperatively. Lidocaine was given, BIS monitoring was performed, and Rocuronium was given to all patients.	PROCEDURES Patients were randomized into one of the two groups. Group 1-revieved Propofol (TCI) TIVA with a goal of BIS monitoring 40-60 and MAP 20% of baseline or greater than 60mmHG for maintenance phase. Group 2 received Thiopental 5mg/kg in addition to Rocuronium and Lidocaine for induction. For maintenance these patients were given Sevoflurane gas with a BIS monitoring 40-60 and MAP 20% of baseline or greater than 60mmHG.

Appendix A

Table A-5

Study Specific Data

Kim, S.H., Lee, J. Y., Lee, S.H., Lim, J.A., Oh, C.S., Yoon, T.G., Yang, J. H., & Yoo, Y.B. (2018). The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: an in vitro analysis. BMC Cancer, 18, 1. https://doi-org.ric.idm.oclc.org/10.1186/s12885-018-4064-8					
AIM/PURPOSE The researchers sought to identify the effect of Propofol TIVA versus Sevoflurane on natural killer cells, cytotoxic T cells, and apoptosis rates in patients undergoing surgery for breast cancer. Additionally, cytokine tumor necrosis factor-α, IL-6, and IL-10 were measured.	DESIGN Single center, prospective, double blind, randomized control trial. Group 1-Propofol (TIVA) Group 2-Sevoflurane	SITE Konkuk Universiry Medical Center, Korea	SAMPLE 44 women undergoing surgery for breast cancer. Group 1- (n=23) Propofol TIVA group Group 2-(n=21) Sevoflurane group	METHODS Patients were randomized into the two groups. Blood samples were obtained prior to induction, 1- hour postoperatively, and 24-hours postoperatively. Anesthesia was induced. BIS monitoring was used on both groups. In addition to the given anesthetic, both groups received Ketorolac for pain management during the anesthetic. Group 1-received Propofol (TCI) TIVA with a goal of BIS 40-60. Group 2- received induction with a Thiopental 5mg/kg, Remifentanil, and Rocuronium for induction. Sevoflurane was administered for maintenance with a goal of BIS 40-60.	PROCEDURES Patients were randomized into one of the two groups. After induction group received Propofol (TCI) TIVA with a goal of BIS monitoring 40-60 and MAP 20% of baseline or greater than 60mmHG for maintenance phase. Group 2- Received Sevoflurane gas with a BIS monitoring 40-60 and MAP 20% of baseline or greater than 60mmHG. Neuromuscular blockade was reversed with neostigmine and glycopyrrolate at the termination of the anesthetic for both groups.

Appendix B

Table B-1
Outcome Data Tables

Sun, L., Wang, B.N., Yan, T., Zhang, G.H., & Zheng, H. (2018). Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: a prospective, randomized and controlled study. *BMC Anesthesiology*, *18*(1), N.PAG. https://doi-org.ric.idm.oclc.org/10.1186/s12871-018-0588-3			
Preoperative Values	***Group 1-TIVA***	***Group 2-Sevoflurane***	***P Value***
VEGF-C	133 (80-205)	105 (87-193)	*p=0.729*
TGF-β	198 (100-304)	197 (131-318)	*p=0.721*
Postoperative Values (24 hours)			
VEGF-C	140 (92-250)	174 (111-281)	*p=0.177*
TGF-β	176 (116-361)	211 (109-308)	*p=0.794*
Pre-Post Changes			
VEGF-C	12 (-8-52)	50 (21-108)	*p=0.008*
TGF-β	13 (-17-51)	3(-30-47)	*p=0.582*
Recurrence Free Survival at 24 months postoperatively	95%	75%	*p=0.221*

Appendix B

Table B-2
Outcome Data Tables

Ito, M., Kadoya, T., Funaoka, Y.,Kawai, A., Kim, R., Wakisaka, M.,Y., Ohtani, S., & Okada, M. (2017). Differences in immune response to anesthetics used for day surgery versus hospitalization surgery for breast cancer patients. *Clinical & Translational Medicine*, *6*(1), 1–8. Doi: 10.1186/s40169-017-0163-4 https://doi-org.ric.idm.oclc.org/10.1186/s40169-017-0163-4		
Changes in Median Values Preoperatively	***Group 1-Day surgery, Lidocaine/Propofol/Pethidine (TIVA) (n=21)***	***Group 2-Hospitalized, Sevoflurane/Propofol, systemic-opioid-based (n=16)***
NK Cell Activity	30.5 ± 9.2	24.5 ± 13.8
CD4/8 T Cell Ratio	1.31 ± 0.32	1.63 ± 0.55
IL6	1.1 ± 0.5	2.0 ± 1.94
Changes in Median Values Postoperatively		
NK Cell Activity	29.0 ± 9.0	31.0 ± 12.3
CD4/8 T Cell Ratio	1.53 ± 0.64	1.23 ± 0.16
IL-6	1.0 ± 0.65	3.9 ± 2.95
Changes in Median Values (24 hours)		
NK Cell Activity	32.0 ± 7.5	25.0 ± 9.5
CD4/8 T Cell Ratio	1.67 ± 0.34	1.61 ± 0.68
IL-6	5.4 ± 1.35	15.3 ± 7.15

Appendix B

Table B-3
Outcome Data Tables

Buggy, D. J, Burns, D., Ní Eochagáin, A., Riedel, B., & Sessler, D. I. (2018). The effect of anaesthetic technique during primary breast cancer surgery on neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and return to intended oncological therapy. *Anaesthesia*, 73(5), 603–611. https://doi-org.ric.idm.oclc.org/10.1111/anae.14207			
Preoperative Median Values	***Group 1-Propofol/Paravertebral TIVA (n=59)***	***Group 2-Sevoflurane/Opioid (n=57)***	***P Value***
White Cell	7.4	7.2	*p=0.850*
Neutrophil	4.7	4.6	*p=0.825*
Lymphocyte	2.0	1.9	*p=0.915*
Platelets	292	265	*p=0.565*
Neutrophil-Lymphocyte Ratio	3.0	4.0	*p=0.850*
Platelet-Lymphocyte Ratio	142	148	*p=0.640*
Postoperative Median Values (Within 72 hours)			
White Cell $\times 10^9.l^{-1}$	9.0	9.0	*p=0.900*
Neutrophil $\times 10^9.l^{-1}$	6.4	6.5	*p=0.885*
Lymphocyte $\times 10^9.l^{-1}$	1.8	1.7	*p=0.860*
Platelets $\times 10^9.l^{-1}$	268	237	*p=0.610*
Neutrophil-Lymphocyte Ratio	3.0	4.0	*p=0.001*
Change in Neutrophil-Lymphocyte Ratio	30%	81%	*p=0.001*
Platelet-Lymphocyte Ratio	148	148	*p=0.885*

Appendix B

Table B-4
Outcome Data Tables

Kim, S.H., Lee, J.Y., Lee., S.H., Oh, C.S., Park, H.J., Piao, L., H., Seo, E.H., & Yoon, T.G. (2018b). Effect of Equipotent Doses of Propofol versus Sevoflurane Anesthesia on Regulatory T Cells after Breast Cancer Surgery. Anesthesiology, 129(5), 921–931. https://doi-org.ric.idm.oclc.org/10.1097/ALN.0000000000002382				
Group 1- Propofol (TIVA) n=99	***Preoperative Value***	***1-Hour Post Procedure***	***24 Hours Post Procedure***	***P Value***
Frequency of CD39 Expression	17.1%	16.7 ± 7.6%	16.9%	*p = 0.680*
Frequency of CD73 Expression	19.4%	18.5%	19.2%	*p = 0.658*
Median Value: Neutrophil-Lymphocyte Ratio	1.55	1.62		*p=0.202*
Group 2- Sevoflurane N=102				
Frequency of CD39 Expression	17.6%	16.5 ± 7.9%	17.6%	*p = 0.680*
Frequency of CD73 Expression	19.0%	19.2%	19.6%	*p = 0.658*
Median Value: Neutrophil-Lymphocyte Ratio	1.76	1.68		*p=0.883*

Appendix B

Table B-5
Outcome Data Tables

Kim, S.H., Lee, J. Y., Lee, S.H., Lim, J.A., Oh, C.S., Yoon, T.G., Yang, J. H., & Yoo, Y.B. (2018a). The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: an in vitro analysis. BMC Cancer, 18, 1. https://doi-org.ric.idm.oclc.org/10.1186/s12885-018-4064-8

	Preoperative Median Value: Group 1- Propofol (TIVA) (n=23)	***Preoperative Median Value: Group 2- Sevoflurane (n-21)***	***P Value***	***1-Hour Post Procedure Median Value: Group 1***	***1-Hour Post Procedure Median Value: Group 2***	***P Value***	***24 Hours Post Procedure Median Value: Group 1***	***24 Hours Post Procedure Median Value: Group 2***	***P Value***
TNF-α	410 (390-470)	404 ± 42	*p=0.175*	390 (390-430)	400 (370-455)	*p=0.953*	420 (390-430)	417 ± 25	*p=0.958*
IL-6	90 (80-100)	90 (90-95)	*p=0.542*	100 (90-100)	90 (90-100)	*p=0.511*	90 (90-100)	90 (90-100)	*p=0.774*
IL-10	490 (450-550)	470 (445-525)	*p=0.430*	490 (440-550)	450 (435-520)	*p=0.340*	470 (430-570)	470 (440-500)	*p=0.960*

Appendix C

Table C-1
Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Sun, L., Wang, B.N., Yan, T., Zhang, G.H., & Zheng, H. (2018). Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: a prospective, randomized and controlled study. *BMC Anesthesiology*, *18*(1), N.PAG. https://doi-org.ric.idm.oclc.org/10.1186/s12871-018-0588-3			
A. Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?	X		
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B. What are the results?			
7. How large was the treatment effect?	83 female patients undergoing surgery for breast cancer removal		
8. How precise was the estimate of the treatment effect?	Significantly higher amounts of VEGF-C released in Sevoflurane group, minor difference in recurrence free survival between groups.		
C. Will the Results Help Locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Appendix C

Table C-2
Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Ito, M., Kadoya, T., Funaoka, Y.,Kawai, A., Kim, R., Wakisaka, M.,Y., Ohtani, S., & Okada, M. (2017). Differences in immune response to anesthetics used for day surgery versus hospitalization surgery for breast cancer patients. *Clinical & Translational Medicine*, *6*(1), 1–8. Doi: 10.1186/s40169-017-0163-4 https://doi-org.ric.idm.oclc.org/10.1186/s40169-017-0163-4			
A. Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?			X
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?			X
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B. What are the results?			
7. How large was the treatment effect?	37 female patients undergoing surgery for breast cancer removal		
8. How precise was the estimate of the treatment effect?	No difference between the two groups		
C. Will the Results Help Locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?		X	
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Appendix C

Table C-3
Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Buggy, D. J, Burns, D., Ní Eochagáin, A., Riedel, B., & Sessler, D. I. (2018). The effect of anaesthetic technique during primary breast cancer surgery on neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and return to intended oncological therapy. *Anaesthesia*, 73(5), 603–611. https://doi-org.ric.idm.oclc.org/10.1111/anae.14207			
A. Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?		X	
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B. What are the results?			
7. How large was the treatment effect?	201 female patients undergoing surgery for breast cancer removal		
8. How precise was the estimate of the treatment effect?	Changes in amounts of immune cells released were similar with propofol and sevoflurane.		
C. Will the Results Help Locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Appendix C

Table C-4
Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Kim, S.H., Lee, J.Y., Lee., S.H., Oh, C.S., Park, H.J., Piao, L., H., Seo, E.H., & Yoon, T.G. (2018b). Effect of Equipotent Doses of Propofol versus Sevoflurane Anesthesia on Regulatory T Cells after Breast Cancer Surgery. Anesthesiology, 129(5), 921–931. https://doiorg.ric.idm.oclc.org/10.1097/ALN.0000000000002382			
A. Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?	X		
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B. What are the results?			
7. How large was the treatment effect?	116 female patients undergoing surgery for breast cancer removal		
8. How precise was the estimate of the treatment effect?	Propofol-paravertebral TIVA attenuated the postoperative increase in the neutrophil-lymphocyte ratio.		
C. Will the Results Help Locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Appendix C

Table C-5
Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist

Kim, S.H., Lee, J. Y., Lee, S.H., Lim, J.A., Oh, C.S., Yoon, T.G., Yang, J. H., & Yoo, Y.B. (2018a). The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: an in vitro analysis. BMC Cancer, 18, 1. https://doi-org.ric.idm.oclc.org/10.1186/s12885-018-4064-8			
A. Are the results of the trial valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, health workers, and study personnel "blind" to treatment?	X		
5. Were the groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B. What are the results?			
7. How large was the treatment effect?	44 female patients undergoing surgery for breast cancer removal		
8. How precise was the estimate of the treatment effect?	No difference in NK cell and CTL counts between groups.		
C. Will the Results Help Locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harms and costs?	X		

Appendix D

Cross Study Analysis

AUTHOR / YEAR	COMPARISONS OR PROTOCOL OF STUDY	OUTCOME/RESULTS	OUTCOME/RESULTS
Study 1 (Sun et al., 2018)	<u>VEGF-C, TGF-β Levels, Recurrence Free Survival</u> **Group 1: TIVA** T0: Prior to procedure T1: 24 hours post procedure T0/T1: Comparison T3: 2 Year Recurrence Free Survival **Group 2: Sevoflurane** T0: Prior to procedure T1: 24 hours post procedure T0/T1: Comparison T3: 2 Year Recurrence Free Survival	<u>VEGF-C Levels</u> **Group 1: TIVA** VEGF-C levels increased from 133 to 140 in the preoperative (T0) to postoperative time (T1). There was a pre/post changes value of 12 when comparing the preoperative value to the postoperative value. **Group 2: Sevoflurane** There was an increase in VEGF-C levels from 105 to 174 in preoperative (T0) to postoperative values (T1). There was a pre-post changes value of 50 when comparing the preoperative value to postoperative value. <u>TGF-β</u> **Group 1: TIVA** TGF-β values decreased from 198 to 176 from T0 to T1. There was a change of 13 when comparing T0 to T1. **Group 2: Sevoflurane** TGF-β values increased from 197 (T0) to 211 (T1). There was a change value of 3 when comparing T0 to T1.	<u>Recurrence Free Survival</u> **Group 1: TIVA** Two patients experienced a recurrence of their cancer. There was a recurrence free survival value of 95% at the two-year mark in this group. **Group 2: Sevoflurane** Six patients had recurrence of their cancer in this group. There was a 78% recurrence free survival rate in this group.

Study 2 (Ito et al., 2017)	Changes in NK Cell activity, Changes in CD4/8 T Cell Ratio, Changes in IL-6 Levels **Group 1: Day surgery, Lidocaine/Propofol/Pethidine (TIVA)** T0: Preoperative T1: Postoperative T2: 24 hours postoperative **Group 2: Hospitalized, Sevoflurane/Propofol, systemic-opioid-based** T0: Preoperative T1: Postoperative T2: 24 hours postoperative	Changes in NK Cell Activity **Group 1: Day surgery, Lidocaine/Propofol/Pethidine (TIVA)** There was a slight decrease in values from 30.5 ± 9.2 (T0) to 29.0 ± 9.0 (T1). Values then increased slightly to 32.0 ± 7.5 (T2). **Group 2: Sevoflurane** Values stayed fairly steady through all time periods, 24.5 ± 13.8 (T0), 31.0 ± 12.3 (T1), and 25.0 ± 9.5 Changes in CD4/8 T Cell Ratio **Group 1: Day surgery, Lidocaine/Propofol/Pethidine (TIVA)** The changes in median value of CD4/8 T Cell ratio increased over all time periods. The median value at T0 was 1.31 ± 0.32 which increased to 1.53 ± 0.64 (T1), and 1.67 ± 0.34 (T2). **Group 2: Sevoflurane** The changes in CD4/8 T Cell median values decreased from 1.63 ± 0.55 (T0) to 1.23 ± 0.16 (T1), and then returned to close to baseline 1.61 ± 0.68 at T2.	Changes in IL-6 Levels **Group 1: Day surgery, Lidocaine/Propofol/Pethidine (TIVA)** Levels remained fairly unchanged, 1.1 ± 0.5 (T0) to 1.0 ± 0.65 (T1), between the first time intervals. There was a sharp increase in levels at T2 with a median value of 5.4 ± 1.35. **Group 2: Sevoflurane** There was an increase in median levels from 2.0 ± 1.94 (T0) to 3.9 ± 2.95 (T1). A larger increase occurred with a median level of 15.3 ± 7.15 at T2.

Study 3 (Buggy et al., 2018)	Amount of White Cells, Neutrophils, Lymphocytes, Platelets, as well as the Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, and Change in Neutrophil-Lymphocyte Ratio **Group1: Propofol/Paravertebral TIVA** T0: Preoperative T1: 24 hours postoperative **Group 2: Sevoflurane/Opioid** T0: Preoperative T1: 24 hours postoperative	White Cell Levels **Group 1: Propofol/Paravertebral TIVA** There was an increase in white cell levels from 7.4 (T0) to 9.0 (T1) **Group 2: Sevoflurane/Opioid** There was an increase in white cell levels from 7.2 (T0) to 9.0 (T1) Neutrophils **Group 1: Propofol/Paravertebral TIVA** There was an increase from 4.7 (T0) to 6.4 (T1). **Group 2: Sevoflurane/Opioid** Levels increased from 4.6 (T0) to 6.5 (T1). Lymphocytes **Group 1: Propofol/Paravertebral TIVA** Levels slightly decreased from 2.0 (T0) to 1.8 (T1). **Group 2: Sevoflurane/Opioid** There was a slight decrease from 1.9 (T0) to 1.7 (T1). Platelets **Group 1: Propofol/Paravertebral TIVA** Levels decreased from 292 (T0) to 268 (T1). **Group 2: Sevoflurane/Opioid** There was a decrease from 265 (T0) to 237 (T1).	Platelet-Lymphocyte Ratio **Group 1: Propofol/Paravertebral TIVA** There was a slight increase from 142 (T0) to 148 (T1). **Group 2: Sevoflurane/Opioid** The value remained the same for both time periods 148 (T0) and 148 (T1). Neutrophil-Lymphocyte Ratio **Group 1: Propofol/Paravertebral TIVA** The value remained unchanged for both time intervals with a value of 3.0. **Group 2: Sevoflurane/Opioid** The value remained unchanged at both time intervals with a value of 4.0 Change in Neutrophil-Lymphocyte Ratio **Group 1: Propofol/Paravertebral TIVA** There was a change in the Neutrophil-Lymphocyte Ratio of 30% for group 1. **Group 2: Sevoflurane/Opioid** There was a change in the Neutrophil-Lymphocyte Ratio of 81%in group 2.

Study 4 (Kim et al., 2018b)	<u>Frequency of CD39 Expression, Frequency of CD73 Expression, and Median Values of Neutrophil-Lymphocyte Ratio</u> **Group 1: Propofol (TIVA)** T0: Preoperative T1:1-hour postoperative T2: 24 hours postoperative **Group 2: Sevoflurane** T0: Preoperative T1: 1-hour postoperative T2: 24 hours postoperative	<u>Frequency of CD39 Expression</u> **Group 1: Propofol (TIVA)** There was a decrease in expression with values decreasing from 17.1% (T0), 16.7 ± 7.6% (T1), to 16.9% (T2). **Group 2: Sevoflurane** There was a decrease in expression from 17.6% (T0) to 16.5 ± 7.9% (T1). Expression returned to baseline of 17.6% at T2. <u>Frequency of CD73 Expression</u> **Group 1: Propofol (TIVA)** There was a decrease in expression from 19.4% (T0) to 18.5% (T1). Expression then increased to 19.2% (T2). **Group 2: Sevoflurane/Opioid** Expression levels remained fairly steady with expression values of 19.0% (T0), 19.2% (T1) and 19.6% (T2).	<u>Median Values of Neutrophil-Lymphocyte Ratio</u> **Group 1: Propofol (TIVA)** Median values remained fairly unchanged with a value of 1.55 at T0 and 1.62 at T1. **Group 2: Sevoflurane** Median Values decreased from 1.76 at T0 to 1.68 at T1.

Study 5 (Kim et al., 2018a)	Amount of TNF-α, IL-6, and IL-10 **Group1: Propofol (TIVA)** T0: Preoperative T1: 1-hour postoperative T2: 24 hours postoperative **Group 2: Sevoflurane** T0: Preoperative T1: 1-hour postoperative T2: 24 hours postoperative	Amount of IL-6 **Group 1: Propofol (TIVA)** The amount increased from 90 (T0) to 100 (T1) and then returned to baseline of 90 at T2. **Group 2: Sevoflurane** The amount remained unchanged for all time periods with a value of 90 (T0, T1, and T2). Amount of IL-10 **Group 1: Propofol (TIVA)** The amount remained unchanged at T0 and T1 with a value of 490, then decreased to 470 at T2. **Group 2: Sevoflurane/Opioid** The amount decreased from 470 (T0) to 450 (T1) and then returned to baseline value of 470 at T2.	Amount of TNF-α **Group 1: Propofol (TIVA)** The amount decreased from 410 (T0) to 390 (T1) and then increased to 420 (T2). **Group 2: Sevoflurane** **The amount decreased from** 404 ± 42 (T0) to 400 (T1) and then sharply increased to 417 ± 25 at T2.